REMARKS

Claims 1-13 are pending and Claim 7 is currently withdrawn.

Claim 1 is amended herein to further enhance clarity by reciting "microreservoirs containing rotigotine free base".

No new matter is added and no change in inventorship has resulted from the proposed amendment.

RESPONSE TO OFFICE ACTION DATED 31 AUGUST 2010

Applicant appreciates the courtesy shown by Examiner Buckley and Examiner Schnizer in the in-person interview on 22 Sept 2010. The following response takes account of that discussion.

1. Rejection under 35 U.S.C. §102(e)/103(a) over Lauterbach

Claims 1–6 and 8–13 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Lauterbach *et al.* (U.S. Patent Application Publication No. 2003/0027793, herein "Lauterbach").

Pending Claim 1 recites: A transdermal delivery system (TDS) comprising a backing layer and a self-adhesive matrix containing rotigotine, wherein the self-adhesive matrix comprises a solid or semi-solid semi-permeable polymer

(1) wherein rotigotine in its free base form is incorporated,
(2) which comprises a multitude of microreservoirs within the matrix, said microreservoirs containing rotigotine free base,
(3) which is permeable to the free base of rotigotine,
(4) which is substantially impermeable to the protonated form of rotigotine, and
(5) wherein the microreservoirs have a maximum diameter that is less than the thickness of the matrix;

and wherein the backing layer is inert to the components of the matrix.

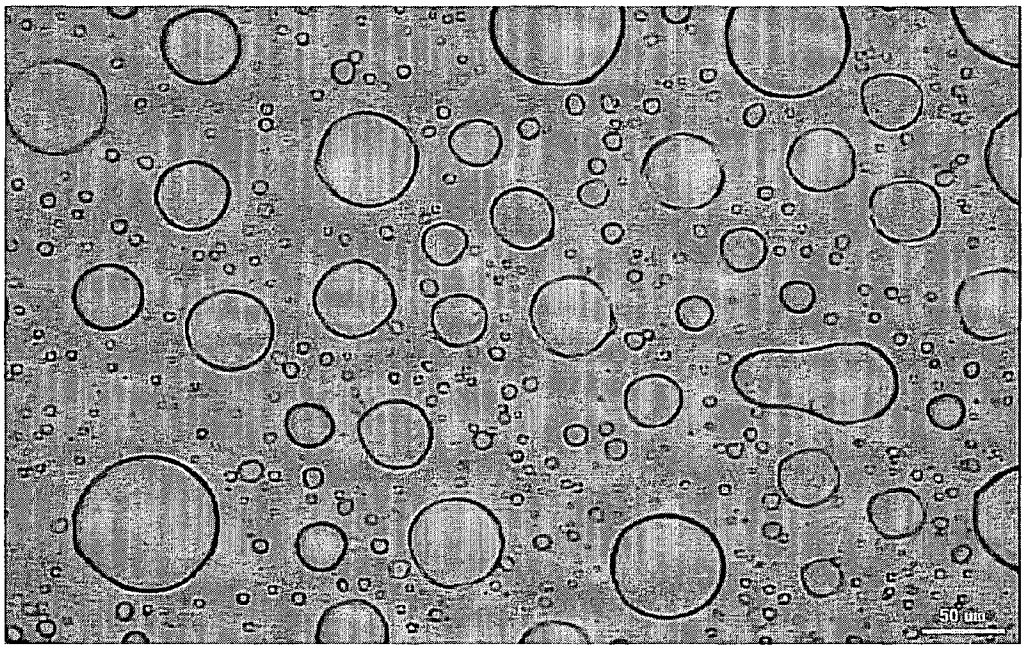
1. Lauterbach does not anticipate Claim 1 (and dependent claims)

The Office has acknowledged that "[r]egarding the microreservoirs and their instantly recited maximum diameter and substantial impermeability to the protonated form of rotigotine as in pending claim 1, Lauterback et al. does not explicitly disclose these characteristics." (31 Aug 2010 Office Action, pg. 4). However, the Office has compared the TDS preparation example in Lauterbach to the present invention and concludes "[s]ince these formulations are

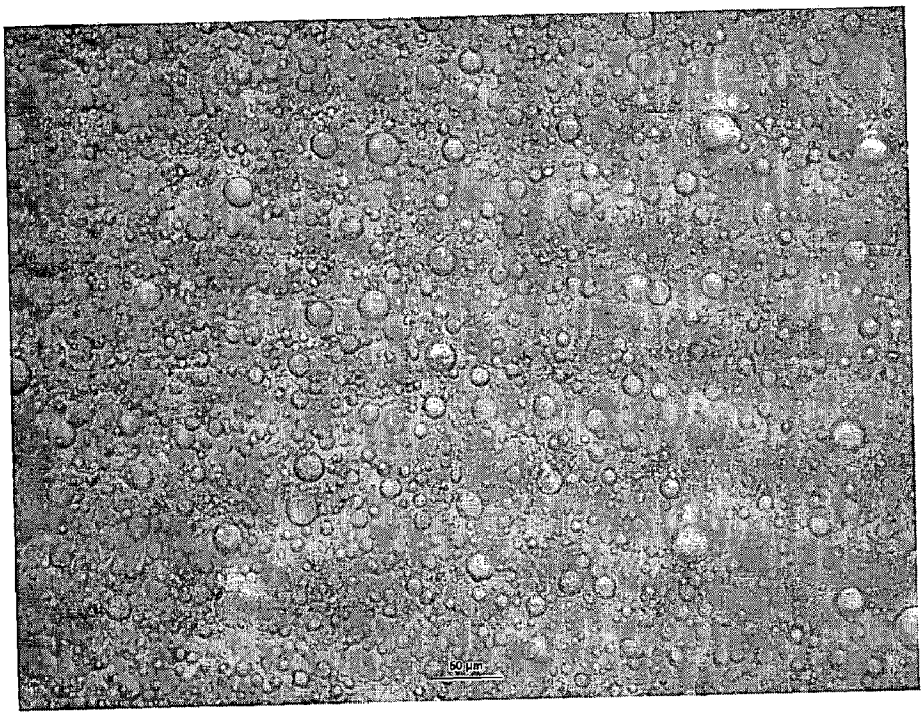
made using the same components and the same method, the formulation of Lauterback is considered to have permeability and microreservoir characteristics as in…pending claim 1, absent evidence to the contrary." *Id.* at pg. 5. Therefore, Applicant presents evidence below that the TDS defined by Applicant's Claim 1 is not anticipated by Lauterbach's disclosure.

At the outset, to clarify, the presently claimed invention is an improvement invention over Lauterbach. Lauterbach does not disclose at least the following Claim 1 element: "**wherein the microreservoirs have a maximum diameter that is less than the thickness of the matrix"**. Applicant has defined "maximum diameter" in the specification as filed at pg. 7, lines 28-30 as "[t]he term 'maximum diameter' is meant to be understood as the diameter of the microreservoirs in one dimension (x-, y-, or z-dimension), which is the largest. (emphasis added) Therefore, each rotigotine free base-containing microreservoir has to be less than the thickness of the matrix since the "largest" diameter is less than the thickness of the matrix.

First, Applicant's specification contains Lauterbach's TDS preparation example as a comparison to demonstrate the present invention's improvement over Lauterbach's TDS. Please see Comparative Example 2 in the specification as filed. Comparative Example 2 is the same TDS preparation in Lauterbach which produced large microreserviors having a maximum diameter larger than the thickness of the matrix. As discussed below, this has an impact on the release profile of rotigotine. A microscopic image of Lauterbach's microreservoirs is depicted in Applicant's Figure 4, and shown below:



Compare Fig. 4 above, with the microscopic image of the present invention in Fig. 5 below.



Second, the table below displays the differences between Lauterbach's TDS

preparation example and Applicant's TDS manufacturing process, thus Lauterbach and the present formulation are not using the same components and method-to-make.

Lauterbach's Preparation Example	**Applicant's Invention Example 1**
Starting material is *rotigotine hydrochloride* and the free base is prepared in situ – meaning that a certain amount of the hydrochloride remains in the TDS	Starting material is crystalline *rotigotine free base*
96% ethanol (comprising certain amount of water)	100% ethanol
Sodium phosphate buffer is used => adding further salt/protons to the solution	No addition of buffer

To clarify further, there is a larger presence of water during manufacture of Lauterbach's TDS, which has two consequences:

i. increases the diameter of the microreservoirs, *i.e.* more water causes bigger microreservoirs which are potentially bigger than the thickness of the TDS; and

ii. some amount of salt will be transferred into the TDS.

These differences will influence size of the microreservoirs and the semi-permeability of the TDS and therefore the rotigotine release profile of the TDS. As can be seen from the figures of the present application, *e.g.* Fig. 3 and 6, Applicant's TDS is an improvement using lower salt content and smaller microreservoirs (less than the thickness of the matrix) to achieve a better release profile for rotigotine. Thus, Applicant's Claim 1 is indeed novel over Lauterbach's disclosure.

Further, Applicant's Claim 1 (and dependent claims) are non-obvious over Lauterbach as well. At the time of the invention, it was very difficult to achieve at least three items:

1. a large enough amount of rotigotine free base as starting material for the improved TDS preparation;
2. a more homogenous distribution for the improved TDS, as can be seen from Applicant's image in Fig. 5 compared to Lauterbach's Fig. 4; and
3. a small enough density.

Also, at the time of the invention, no one knew what the impact of size and distribution would be on rotigotine's release rate through skin. Figs. 3 and 6 display the improvement in rotigotine release/permeation compared to Lauterbach's TDS. This improvement could not have been predicted by the ordinary artisan. Lauterbach certainly does not teach or suggest how to achieve this improvement either. Therefore, Lauterbach does not establish a presumption of *prima facie* obviousness over Applicant's Claim 1 (or any claims depending therefrom). Applicant respectfully requests reconsideration and withdrawal of the present 102(e)/103(a) rejection over Claims 1–6 and 8–13.

2. <u>Rejection under 35 U.S.C. §103(a) over Chien and Müller</u>

Claims 1-4, 10 and 11 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,788,983 to Chien, et al. ("Chien") in view of International Patent Publication No. WO1999/49852, using U.S. Patent No. 6,884,434 to Müller, *et al.* as an English-language equivalent ("Müller"). This rejection is respectfully traversed.

Chien, the primary document relied upon, reports a transdermal dosage unit for administration of one or more pharmaceuticals, particularly a combination of progestational and estrogenic steroids, simultaneously at controlled and variable rates of transdermal delivery.

Müller is relied upon for rotigotine's use in a silicone adhesive TDS.

The Office asserts "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to implement rotigotine free base and silicone adhesives as taught by Muller et al. in the transdermal devices of Chien et al. One would have been motivated to do so since Chien teaches that any pharmaceutical agent can be

delivered and since Muller teaches rotigotine actives administered by silicone adhesives." (31 Aug 2010 Office Action, pg. 8) Applicant respectfully disagrees and submits that a presumption of *prima facie* obviousness has not been established based on Chien and Müller for at least the following reasons.

1. *Failure to Teach All Elements of Claim 1*

It is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because the alleged combination fails to teach all elements of Claim 1. Particularly, Chien and Müller do not disclose, teach or suggest the following elements recited in Claim 1:

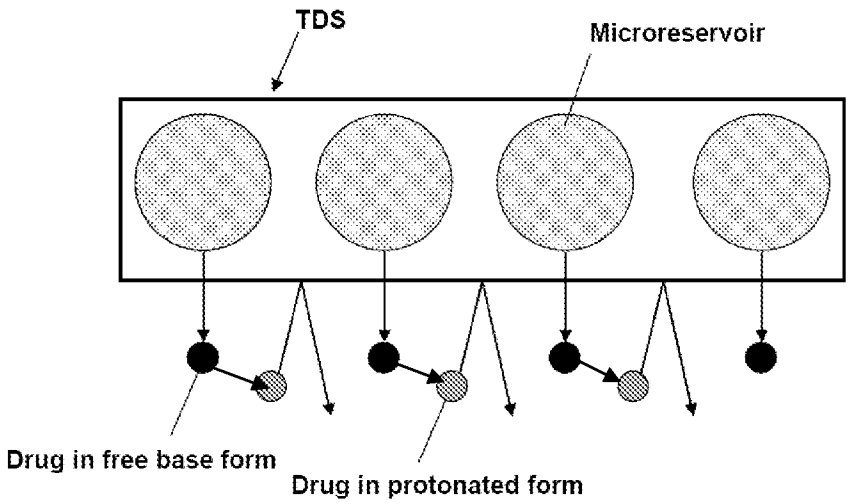
a. *"wherein rotigotine in its free base form is incorporated"*

Although Chien provides a large laundry list of possible drugs, including broad classes of drugs, that may or may not work in Chien's dosage unit, Chien makes no mention or differentiation of drugs being in free base form versus protonated form, nor specifically "microreservoirs containing rotigotine in free base form". Müller does not cure this deficiency either.

b. *"the microreservoirs...have a maximum diameter less than the thickness of the matrix"*

Neither Chien nor Müller teach that the maximum diameter of microreservoirs should be less than the thickness of the matrix. The pending 31 Aug 2010 Office Action states at p. 8: "Additionally, since the microreservoirs are dispersed in the polymeric adhesive, the diameter of the microreservoirs necessarily would have been less than the thickenss of the adhesive matrix." This conclusion is mistaken. Just because microreservoirs are dispersed in a matrix does not mean that their maximum diameter is less than the thickness of the matrix. Microreservoirs can be dispersed throughout a matrix but still come into contact with the outer edge of the matrix, and thus come into contact with the skin. Whereas, if the maximum diameter of the microreservoirs, *i.e.* the largest diameter as defined by Applicant, is less than the thickness of the matrix, this avoids contact of the free base drug with the skin. This is an important feature of Applicant's microreservoirs which took a great amount of experimentation to determine and achieve. It is an important feature because one wants to

avoid having the free base drug come in direct contact with slightly acidic skin which causes protonation of the free base and unwanted back diffusion of the drug. This structural element of Claim 1 and concept is not taught anywhere in Chien or Müller. To help illustrate this concept, below is an exaggerated schematic:



2. *Chien is not enabling*

Further, it is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because Chien, the primary document relied upon, is not enabled. Although Chien provides a laundry list of possible drugs and classes of drugs at Col 11, clearly the ordinary artisan would not believe that each drug mentioned and each drug in each class mentioned would work in Chien's dosage unit. More importantly, the ordinary artisan would find it incredible that every drug in each class mentioned would work in Applicant's claimed dosage unit, which had to be specifically developed to improve delivery of weakly basic amine drugs in free base form. In support of this conclusion:

- First, all the examples in Chien are directed to hormone drugs. Almost the entire description is directed to these hormone drugs, and mostly in combination, except for the laundry list at Col 11. There is not even any mention of the effects free base vs. protonation have on drug delivery. In fact, many of the drugs in Chien's laundry list are salts (hydrochlorides) and thus

are charge neutral. They do not have a pair of uncoupled electrons and thus would not work in Applicant's TDS. If anything, Chien may represent a mere invitation to experiment with the different classes of drugs. It is well known that such invitation does not establish a *prima facie* case obviousness and the amount of experimentation that would need to be done from a reading of Chien is clearly undue.

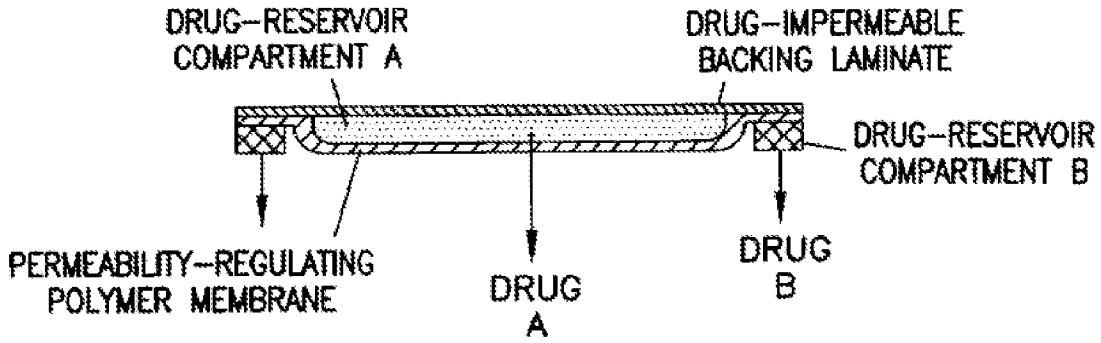
- Second, even the U.S. Examiner during prosecution of the Chien patent recognized that Chien's disclosure was not enabling for all the drugs he attempted to claim and thus Chien had to amend his claims to a limited Markush group of hormone drugs in order to obtain allowance. Please see Chien Final Office Action dated 20 March 1997 and Chien's response dated 28 May 1997.

3. *Chien Did Not Even Recognize the Problem, Much Less Provide Any Reasonable Guidance Toward Applicant's Improved TDS*

Further, it is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because an ordinary artisan reading Chien does not find any reasonable guidance on how to improve transdermal drug delivery of weakly basic amine drugs in free base form, and moreover how to arrive at Applicant's claimed TDS to solve this problem. Applicant respectfully submits that when making an obviousness determination "[a] prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention" See MPEP 2141.03 (emphasis in original). When read "as a whole", Chien represents an extremely broad disclosure and reports an abundance of embodiments, most of which lead away from Applicant's TDS. Below is just an example of a number of selections an ordinary artisan would have to make reading Chien to arrive at Applicant's claimed TDS:

(1) Chien's dosage unit can comprise mono- or multi-regional reservoir compartments. One would have to select mono-regional which goes against Chien's focus on multi-regional reservoir compartments and Chien's focus on

simultaneous administration of hormone drugs to achieve a synergistic effect. Below is the exemplified embodiment in Chien (Fig. 1):



(2) One also has to select between macroreservoirs and microreservoirs;

(3) If one selects microreservoirs (which do not appear to be defined by Chien), one would also have to select between an adhesive polymer, elastomeric polymer or gelling polymer;

(4) One would then have to select rotigotine which is not reported anywhere in Chien;

(5) One would then have to select rotigotine free base which is not reported anywhere in Chien; and

(6) Determine an adhesive polymer that can provide the claimed semi-permeability (*i.e.* be permeable to the drug in free base form and substantially impermeable to the protonated form)

Clearly, this constitutes too many compounded, sequential selections from a vague disclosure to teach Applicant's claimed TDS. Where is the guidance to make any one of these specific selections to lead an ordinary artisan to Applicant's Claim 1, especially in view of Chien's focus on a multi-component TDS? Müller provides no guidance as Müller does not mention how to improve a rotigotine microreservoir TDS. In this case such a multi-step selection, without any guidance on which selections to make, clearly constitutes an unreasonable amount of hindsight using guidance from Applicant's specification to arrive at the claimed invention. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where

the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." In re O'Farrell, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009), *emphasis added.*

4. *No motivation to modify Chien*

Further, it is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because there is no motivation to modify Chien from either the art in general or Müller to arrive at Applicant's Claim 1.

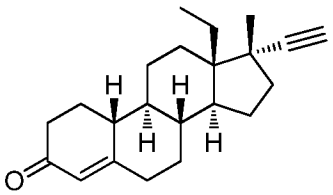
a. Differences between Chien's TDS and Applicant's TDS

First, there are so many differences between Chien and the present invention, that one of ordinary skill would not even look to Chien for modification. Applicant has put these differences into the table below for easy demonstration.

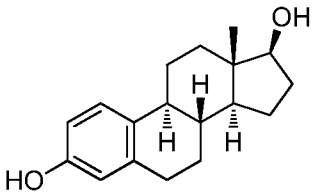
Chien's TDS	**Applicant's TDS**
Multi-component dosage unit with liquid macro- or microreservoirs	Monolithic matrix with solid and/or semi-solid microreservoirs
Multi-regional or mono-regional drug release; if multi-regional then one drug can be released from a liquid macroreservoir or microreservoir	Drug-in-adhesive type structure
Uses a permeability regulating polymer membrane separate from an adhesive. Chien even states in prosecution that "[t]he present invention is a transdermal dosage unit having an impervious backing layer and a reservoir layer having a reservoir compartment region and an outer wall. The reservoir compartment region contains a liquid medium in which one or more pharmaceuticals are dissolved. The outer wall of the reservoir layer is a permeability-	Uses a self-adhesive matrix which functions as both adhesive and enables selective permeation of amine-functional drug

regulating polymer membrane…" *See* Chien response to Office Action dated 2 April 1996 at passage bridging p. 5-6, emphasis in original.	
Developed for simultaneous delivery of steroidal hormone drugs – *i.e.* non-ionizable compounds	Developed for delivery of amine-functional drugs, *i.e* ionizable compounds
No drug ionization discussed, thus no matrix permeability which distinguishes between amine-functional drug in free base form versus protonated form	Self-adhesive matrix with dispersed microresevoirs has desired permeability characteristics for amine-functional drugs
Uses polar solvents, such as ethanol:water mixtures to dissolve hormone drug (See examples)	Volatile solvents including water are substantially removed during manufacture to get solid and/ or semi-solid microreservoirs. Too much water content in the matrix causes the protonated (salt) form of the amine-functional drug to be formed. Protonated form of the amine-functional drug can not be released from the matrix

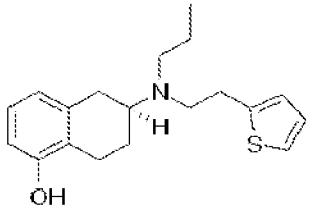
Further, the difference between Chien and Applicant's invention is even clearer when the compounds described in Chien are considered. As can be seen from the structures drawn below, levonogestrel and estradiol have a very different chemical make-up from that of rotigotine:



Levonorgestrel



Estradiol



Rotigotine

Levonorgestrel and estradiol are both steroids and do not have any nitrogen-containing functional groups capable of having an uncoupled electron pair, characteristic of an amine. Neither levonorgestrel nor estradiol have protonatable groups that could form a protonated, salt form. On the other hand, rotigotine is non-steroidal and contains a tertiary amine.

Rotigotine can form a free base or a protonated, quaternary ammonium salt, a feature lacking in each levonorgestrel and estradiol.

b. Differences in Utility between Chien's TDS and Applicant's TDS

Further, there are many differences in utility between Chien's TDS and Applicant's TDS. Therefore, why would the ordinary artisan look to Chien to determine how to improve a rotigotine microreservoir TDS? Chien's TDS is a trandermal absorption dosage unit mainly for use with multiple drugs. Chien is particularly focused on transdermal administration of hormone combinations, such as progestational and estrogenic steroids. Chien's asserted utility is to provide simultaneous absorption of the multiple drugs at different or variable dosage rates and at relatively constant permeation profiles to achieve a synergistic effect between the multiple drugs.

In contrast, Applicant's TDS was developed to enhance delivery of weakly basic amines to and across the skin by preventing back diffusion, offering continuous delivery of the active compound across the stratum corneum not only via the more common lipophilic route (*e.g.* intercellular) but also through hydrophilic pores. Applicant discovered a matrix composition with the desired permeability characteristics that effectively delivers free base amines as opposed to their protonated form through a subject's skin.

c. Modification of Chien to Applicant's TDS Would Not Fulfill Chien's Stated Objective

Lastly, when read "as a whole", Chien focuses on a TDS system comprising at least four distinct elements – see Chien's Figure 1 reproduced above. To arrive at the claimed invention, it would be necessary to modify Chien's TDS to be a system comprising a monolithic component, e.g. by singling out one "component", to be combined with Müller. However, one of ordinary skill in the art would not have been motivated to use just one component of Chien's system because such use would not achieve the goal of Chien, *i.e.,* simultaneous administration of multiple pharmaceuticals. Thus, it would not have been obvious to separate, for example, "drug-reservoir compartment B" from the TDS of Chien and modify the separated "compartment" with the teaching of Müller in order to arrive at a TDS

having all of the characteristics of Claim 1.

It should be noted that Chien describes throughout the specification two key structural features: (1) that its TDS is designed to administer multiple pharmaceuticals, and (2) "drug-reservoir compartment B" is integrated into the TDS. For example, Chien states in Col. 2, lines 20-24 that "it is desired to provide improved methods of administration of pharmaceuticals, including the simultaneous administration of multiple pharmaceuticals with different pharmacological activities" To meet this goal, one would need to use the entire TDS described by Chien, *i.e.*, a TDS having at least two drug-reservoir compartments, each of which contain a pharmaceutical with a different pharmacological activity, not just "drug-reservoir compartment B". As stated above, to modify Chien's system to only "drug-reservoir compartment B" would not accomplish Chien's goal (nor does this isolated element meet the characteristics of Claim 1). Therefore, it would not have been obvious for a person having ordinary skill in the art to modify Chien to a system comprising a single self-adhesive matrix containing microreservoirs with rotigotine in free base form, wherein the self-adhesive matrix functions as both an adhesive and permeability controller. For at least this further reason, a presumption of *prima facie* obviousness has not been established for Claim 1 over Chien and Müller.

3. <u>Rejection under 35 U.S.C. §103(a) over Chien, Müller and Pfister</u>

Claim 5 stands rejected under 35 U.S.C. §103(a) over Chien in view of Müller and in further view of U.S. Patent No. 5,232,702 to Pfister *et al.* (herein "Pfister"). This rejection is respectfully traversed.

Claim 5 depends directly from Claim 1, and thus include all features of Claim 1. The present rejection over Chien in view of Müller and Pfister has the same issues as the combination of Chien and Müller discussed above in Section 2 of this response. Pfister does not teach or suggest microreservoirs containing rotigotine in free base form which have a maximum diameter less than the thickness of the matrix nor a matrix which is permeable to rotigotine in free base form and substantially impermeable to rotigotine in protonated form.

Thus, the deficiencies of the alleged combination of Chien and Müller are not supplemented by Pfister.

For at least these reasons, a presumption of *prima facie* obviousness has not been established for Claim 5 over the alleged three-way combination. Thus, reconsideration and withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Chien, Müller, Pfister and Kosal

Claim 6 stands rejected under 35 U.S.C. §103(a) over Chien in view of Müller, Pfister and in further view of U.S. Publication No. 2003/0065086 (herein "Kosal"). This rejection is respectfully traversed.

Claim 6 depends indirectly from Claim 1, and thus include all features of Claim 1. The present rejection over Chien in view of Müller, Pfister and Kosal has the same issues as the combination of Chien and Müller discussed above in Section 2 of this response. Kosal does not teach or suggest microreservoirs containing rotigotine in free base form which have a maximum diameter less than the thickness of the matrix nor a matrix which is permeable to rotigotine in free base form and substantially impermeable to rotigotine in protonated form. Thus, the deficiencies of the alleged combination of Chien and Müller are not supplemented by Kosal.

5. Double Patenting

A. Provisional Obviousness-Type Double patenting over Serial No. 10/627,990 in view of Müller

Claims 1–6 and 8–13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 1, 2, 10-13, 15-18 and 20-23 of copending application Serial No. 10/627,990, in view of Müller. This rejection is provisional because the allegedly conflicting claims have not yet been patented.

The present rejection is respectfully traversed, at least for the reason that the present application has an earlier filing date (22 July 2003) than the reference application (28 July

2003), and therefore, when issued as a patent, will expire before any patent that issues from the reference application. Rejection for double patenting is warranted only where "issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent" (MPEP 804.II.*B*.1). That is not the case here.

Applicant notes that a terminal disclaimer was filed in the '990 application on 29 July 2008.

Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

B. Provisional Obviousness-Type Double patenting over Serial No. 10/139,894

Claims 1, 3-6, 8 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 15, 17, 18, 19 and 27-30 of copending application Serial No. 10/139,894 (Lauterbach, applied in the present 102(e)/103(a) rejection). This rejection is provisional because the allegedly conflicting claims have not yet been patented.

Applicant submits that Claims 1, 3-6, 8 and 9 claim a non-obvious improvement over Lauterbach for at least the reasons stated in Section 1 of the present response. Applicant's Claim 1 improved TDS is structurally different from Lauterbach's TDS; and there is no teaching or suggestion found in Lauterbach to arrive at Applicant's improved TDS. Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

6. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the Application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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